Synthesis and biological evaluation of some 1, 3, 4-thiadiazoles

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Abstract

Thiadiazoles and their derivatives exhibit a wide variety of biological activities like antidiabetic, anti inflammatory, anti-convulsant etc.In the present study we have synthesized some substituted thiadiazoles. The structures of these synthesized compounds were confirmed by IR, NMR and CHN analysis. All the values and results of this spectral and elemental analysis are found to be in the normal range. These compounds were evaluated for various biological activities like Anti-diabetic, anti-inflammatory, anti-fungal activity.

Key words: 1, 3, 4-thiadiazoles; antimicrobial; anti-inflammatory; antidiabetic activity.

Introduction

Diabetes mellitus is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetic, acting jointly. The underlying causes of diabetes are the defective production or action of insulin, a hormone that controls carbohydrate, fat and protein metabolism. Characteristically diabetes is a long-term disease with variable clinical manifestations and progression, chronic hyperglycemia from whatever cause, leads to a number of complications including cardiovascular such as hypertension, renal, neurological such as anxiety, stress, ocular and other such inter-current infections. Diabetes Mellitus is a condition in which the pancreas no longer produces enough insulin or cells stop responding to insulin that is produced, so that glucose in the blood cannot be absorbed in to the cells of the body. Symptoms include frequent urination, lethargy, excessive thirst, and hunger. The treatment includes changes in diet, oral medications and in some cases daily injection of insulin. A large number of 1, 3, 4-thiadiazoles have been reported to be

antifungal, antibacterial and antileukemic agents.[1,2].These observations promoted us to synthesis the title compound with presumption that incorporation of aromatic amines and thiazolidinones nuclei would produce new compounds with significant antidiabetic properties. Lifestyle changes including weight loss and increased activity are the primary recommendations for treatment of type II diabetes. However, because of the progressive nature of the disease, the treatment of type 2 diabetes usually requires the stepwise introduction of oral hypoglycemic drugs followed by insulin. 1, 3, 4-thiadiazoles and their derivatives exhibit a wide variety of biological activities like antidiabetic, anti inflammatory, anti-convulsants1, 2, 3 etc.The synthesized compounds were evaluated for various biological activities like Anti-diabetic, anti-inflammatory, anti-microbial activity.

Experimental Section

Antibacterial activity: *[3, 4]*

The compounds were tested in-vitro for their antibacterial activity against two microorganisms viz. *Escherichia coli* (NCTC 10418), and *Staphylococcus aureus*(NCTC 6571) which are pathogenic in human beings by Cup-plate agar diffusion method using Nutrient agar.

Antifungal activity: *[3, 4]*

The compounds were tested in-vitro for their antifungal activity against *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16404) by Cup-plate agar diffusion method using Sabouraud-Dextrose agar.

Table No.1 : Antibacterial and Antifungal activities of the synthesized compounds

SL. No.	Compd.	Zone of inhibition at 100 mcg/mL (in mm.)			
		E.coli	*S. aureus*	*A. niger*	*C. albicans*
1	**A_1**	18	19	18	19
2	**A_2**	12	15	20	21
3	**A_3**	**22**	**23**	**24**	**24**
4	**A_4**	15	16	17	18
5	**A_5**	17	19	19	20
6	**A_6**	**23**	**23**	12	15
7	**A_7**	20	21	21	22
8	**A_8**	**23**	**23**	**24**	**25**
9	**A_9**	**22**	**23**	19	20
10.	**A_{10}**	17	16	17	16
11.	**A_{11}**	16	12	19	18
12.	**A_{12}**	15	14	20	19
Std.	Norfloxacin	**23**	**24**	--	--
Std.	Griseofulvin	--	--	**25**	**26**

Compounds **A_3, A_6, A_8, A_9** have shown promising antibacterial activity. Norfloxacin was used as standard drug.Compounds **A_3, A_8** have shown promising antifungal activity. Griseofulvin was used as standard drug.

***Antiinflammatory activity*:** [5, 6]

The activity was performed by Carrageenan induced rat hind paw edema method.

Table No. 2: Effect of synthesized compounds and Diclofenac Sodium on Carrageenan Induced rat paw oedema by oral administration

S.No	Compound (100mg/kg)	Mean Paw oedema volume (ml)± SE			
		0 hr	1st hr	2nd hr	3rd hr
1	Control	3.72 ± 0.019	4.1 ± 0.094	4.64 ± 0.062	4.83 ± 0.23
2	Standard (Diclofenac Sodium)	3.57 ± 0.070	3.73 ± 0.108	3.77 ± 0.13	3.79 ± 0.17**
3	**A1**	3.42 ± 0.16	4.10 ± 0.23	3.93 ± 0.07	4.15 ± 0.099**
4	**A3**	3.43 ± 0.15	4.06 ± 0.21	3.86 ± 0.087	4.09 ± 0.088**
5	**A5**	3.43 ± 0.14	4.10 ± 0.23	3.91 ± 0.081	4.12 ±0.096**
6	**A7**	3.40 ± 0.16	3.97 ± 0.21	3.87 ± 0.083	4.13 ± 0.10**
7	**A8**	3.47 ± 0.09	3.92 ± 0.18	3.85 ± 0.090	4.09 ± 0.10**
8	**A9**	3.23 ± 0.08	3.96 ± 0.25	3.96 ± 0.054	3.93 ± 0.057**
9	**A10**	3.23 ± 0.06	3.91 ± 0.25	3.98 ± 0.051	4.02 ± 0.060**
10	**A12**	3.50 ± 0.95	4.02 ± 0.25	3.75 ± 0.017	3.95 ± 0.11**

* $p < 0.05$ Non Significant
** $p < 0.01$ Significant
* ** $p < 0.0001$ (ANOVA followed by Dunnet't' test

***Antidiabetic activity:** [7]*

The compounds synthesized during the present work were subjected to antidiabetic activity for possible preliminary pharmacological screening. Using wistor albino rats by Alloxan induced tail tipping method.

Table No: 3 : Antidiabetic activity of Synthesized compound

Drug	Blood glucose level mg/dl (Mean ± SE)			
	0 h	**1 h**	**3 h**	**6 h**
Control	123.3± 6.00	120.7± 5.54	122.3± 5.81	123.0± 6.4
Glibenclamide	385.8±21.37	230.8±12.35**	156.8±10.87**	93.4±4.986**
A_1	311.6±5.95	268.2±1.88**	212.8±2.95**	166.4± 2.15**
A_2	294.2±20.6	265±19.30ns	198.4±22.14*	168.6±20.68**
A_5	284.6±10.44	274.6±10.27ns	220±10**	160.2±7.14**
A_6	289±15.3	277.8±14.6ns	186.4±12.10*	129±10.74*
A_7	305±27.29	294.8±24.33ns	202.6±11.83**	143.2±10.71**
A_8	300.6±15.63	204.2±15.24**	145±11.79**	103.4±6.86**
A_{10}	340.2±18.27	284±18.31**	248±15.54**	228.2±5.37**

Note: Standard Drug: Glibenclamide
p<0.05 *, p<0.01**, Statistical ANOVA followed by dunnet't' test when compared with
0 hour reading. The drug **A_8**, have shown significant antidiabetic activity. The drug **A_1**, **A_5**, **A_{10}**, have shown moderate antidiabetic activity on oral administration.

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, DMSO *d6* as internal standard. Combustion analyses were found to be within the limits of permissible errors.

Scheme

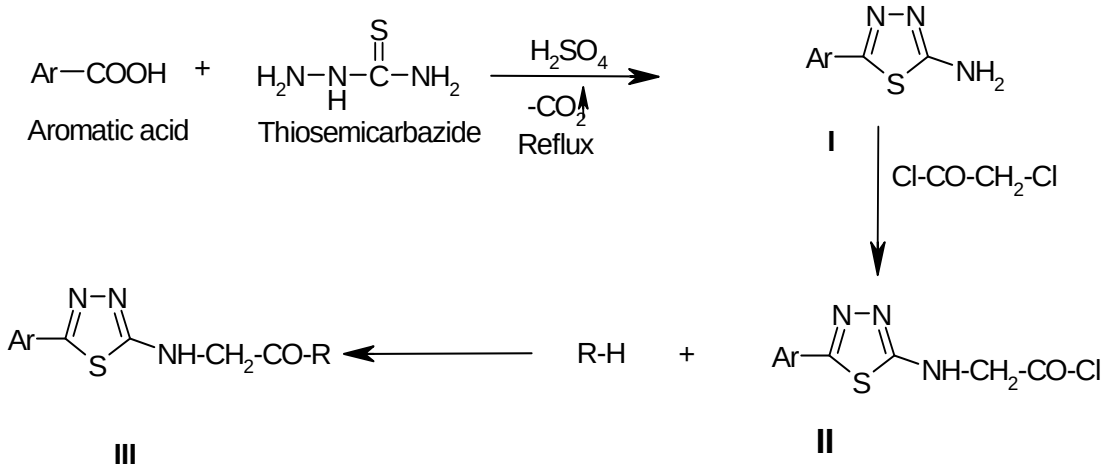
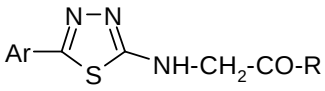
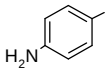
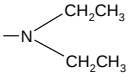
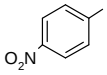
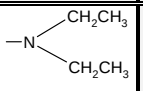
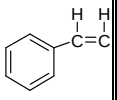
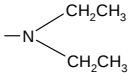
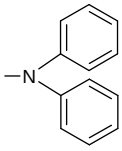
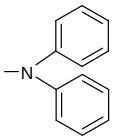
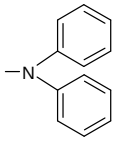
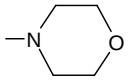
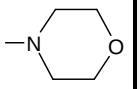
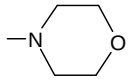
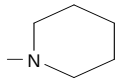
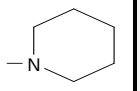
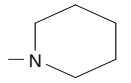


Table No. 4: Synthesized compounds



	Ar	R		Ar	R		Ar	R
A_1			**A_5**			**A_9**		
A_2			**A_6**			**A_{10}**		
A_3			**A_7**			**A_{11}**		
A_4			**A_8**			**A_{12}**		

Procedures for synthesis: [1,2]

Synthesis of 2-amino-5-aryl-1, 3, 4-thiadiazole I

A mixture of thiosemicarbazide (0.1mole), aryl carboxylic acid (0.1 mole), & conc. Sulphuric acid (10 drops) was refluxed for 1 hr & poured onto crushed ice. The solid separated out was filtered, washed with water & recrystallized from ethanol.

Synthesis of substituted N-(5-aryl-1, 3,4-thiadiazole-2-yl)-2-chloroacetamide (II)

Substituted amino compounds (0.5mol) were dissolved in glacial acetic acid (25ml) containing 25ml of saturated solution of sodium acetate. In case the substance did not dissolve completely, the mixture was warmed the solution was cooled in ice bath with stirring. To this chloroacetyl chloride was added drop wise (0.06mol) so that vigorous reaction did not take place. After half an hour white product separated and filtered. The product was washed with 50% aqueous acetic acid and finally with water. It was purified by recrystallization from absolute alcohol.

Synthesis of N-(5-(4-aminophenyl)-1, 3, 4-thiadiazole-2-yl)-2-(diethyl amino) acetamide (A_1)

A mixture of N-(5-(4-aminophenyl)-1,3,4-thiadiazole-2-yl)-2-chloroacetamide 0.01 mol is taken in 25ml of abs. alcohol and 0.01mol of Aryl derivatives was added and refluxed for 4hr. It was purified by recrystallization from aqueous alcohol. The compounds **A_2-A_{12}** were synthesized following a similar procedure.

Table no.5: Analytical data of the synthesized compounds

Compd.	Mol. Formula	Mol. Wt.	Yield %	m.p. ° C	Elemental analyses Calcd. (Found)		
					C	H	N
A_1	$C_{14}H_{19}N_5OS$	305.40	64	218-220	55.06	6.27	22.93
A_2	$C_{22}H_{19}N_5OS$	401.48	67	197-199	65.81	4.77	17.44
A_3	$C_{14}H_{17}N_5O_2S$	319.38	72	229-231	52.65	5.37	21.93
A_4	$C_{15}H_{19}N_5OS$	317.41	65	206-208	57.68	4.52	22.42
A_5	$C_{14}H_{17}N_5O_3S$	335.38	68	159-161	50.14	5.11	20.88
A_6	$C_{22}H_{17}N_5O_3S$	431.47	76	168-170	61.24	3.97	16.23
A_7	$C_{14}H_{15}N_5O_4S$	349.37	72	198-200	48.13	4.33	20.05
A_8	$C_{15}H_{17}N_5O_3S$	347.39	63	123-25	52.62	3.53	20.46
A_9	$C_{16}H_{20}N_4OS$	316.42	68	117-119	60.73	6.37	17.71
A_{10}	$C_{24}H_{20}N_4OS$	412.51	62	110-112	69.88	4.89	13.58
A_{11}	$C_{16}H_{18}N_4O_2S$	330.40	65	120-121	58.16	5.49	16.96
A_{12}	$C_{17}H_{20}N_4OS$	328.43	58	108-110	63.14	4.68	17.32

The combustion analysis of compounds synthesized is within the limits of permissible errors.

Spectral data

A_1: IR Bands (cm^{-1}): 3469.0; NH-str; 3062.4 Ar-CH-str; 1604.7 C=O-str; 1255.6 C-N-str; 612.7 C-S-str; **^{1}H NMR (δ ppm):** 7.49 4H,Ar-CH; 5.82 2H, NH_2 ; 2.891H, NH; 2.17 6H, $2CH_3$;2.59-2.60 6H,$3CH_2$.

A_2: IR Bands (cm^{-1}):3382.9; NH-str; 3052.5 Ar-CH-str; 1600.8 C=O-str; 1244.6 C-N-str; 617.2 C-S-str.

A_3 : IR Bands (cm^{-1}):3432.6; NH-str; 3010.3 Ar-CH-str; 1602.8 C=O-str; 1249.8 C-N-str; 617.5 C-S-str.

A_4 : IR Bands (cm^{-1}):3464.2; NH-str; 3092.5 Ar-CH-str; 1604.7 C=O-str; 1255.6 C-N-str; 607.5 C-S-str. **^{1}H NMR (δ ppm):**7.71-7.76 4H,Ar-CH; 6.54-6.58 2H, NH_2 ; 3.85 1H, NH; 2.13-2.18 6H, $2CH_3$;1.22-2.18 6H,$3CH_2$.

A_5 : IR Bands (cm^{-1}): 3114.5 Ar-CH-str; 1606.7 C=O-str; 1541.0 NO_2 str;1280.6 C-N-str; 619.1 C-S-str.

A_6 : IR Bands (cm^{-1}): 3114.8 Ar-CH-str; 1606.7 C=O-str; 1541.0 NO_2 str;1280.5 C-N-str; 617.2 C-S-str. **^{1}H NMR (δ ppm):**6.83-8.28 14H Ar-CH; 3.73 1H, NH ;2.97 2H, CH_2.

A_7 : IR Bands (cm^{-1}): 3114.8 Ar-CH-str; 1606.6 C=O-str; 1541.0 NO_2 str;1280.6 C-N-str; 607.5 C-S-str. **^{1}H NMR (δ ppm):**8.08-8.29 4H Ar-CH; 5.82 1H, NH ;3.25-3.74 10H, 5 CH_2.

A_8 : IR Bands (cm^{-1}): 3114.8 Ar-CH-str; 1606.6 C=O-str; 1541.0 NO_2 str;1278.7 C-N-str; 619.1 C-S-str.

A_9 : IR Bands (cm^{-1}): 3023.5 Ar-CH-str; 1695.4 C=O-str; 1629.7 C=C str;1286.4 C-N-str; 621.0 C-S-str.

A_{10} : IR Bands (cm^{-1}): 3023.6 Ar-CH-str; 1684.6 C=O-str; 1629.7 C=C str;1286.4 C-N-str; 619.1 C-S-str.

A_{11} : IR Bands (cm^{-1}): 3023.6 Ar-CH-str; 1692.1 C=O-str; 1649.3 C=C str;1286.4 C-N-str; 621.0 C-S-str.

A_{12} : IR Bands (cm^{-1}): 3023.6 Ar-CH-str; 1701.7 C=O-str; 1627.8 C=C str;1286.4 C-N-str; 621.1 C-S-str.

Results and Discussion

The synthesized compounds were subjected to various antibacterial, antifungal and anti-inflammatory and antidiabetic activities by the standard methods.
All the compounds were screened for antibacterial activity. However the compounds **A_3, A_6, A_8, A_9** have shown promising antibacterial activity, while the remaining compounds have also shown moderate antibacterial activity, when compared with the standard drug Norfloxacin against.

All the compounds were also screened for antifungal activity. However compounds **A_3, A_8** have shown promising antifungal activity, while the remaining compounds have also shown moderate antifungal activity, when compared with the standard drug Griseofulvin. All the compounds in addition were also screened for anti-inflammatory activity by winter et al method with standard drug (Diclofenac Sodium). However Compounds **A_3, A_4, A_7, A_8& A_9** have shown promising anti-inflammatory activity.

The synthesized compounds were screened for their antidiabetic activity by Alloxan induced tail tipping method. The Albino rats of either sex weighing between 150-200 g were selected. The blood glucose level was induced and the study was carried out in six difference groups. The drug **A_8** has shown significant antidiabetic activity and compounds **A_1, A_2, A_5** have shown moderate antidiabetic activity.

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